

PCT

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number  
**WO 2005/080403 A2**

- (51) International Patent Classification<sup>7</sup>: C07F 5/02, C07D 401/14
- (21) International Application Number: PCT/GB2005/000567
- (22) International Filing Date: 17 February 2005 (17.02.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
0403744.6 20 February 2004 (20.02.2004) GB
- (71) Applicant (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only): ASTRAZENECA AB [SE/SE]; S-SE-151 85 Sodertalje (SE).
- (71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): BUTLIN, Margaret, Anne [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). BUTLIN, Roger,
- John [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). HOGAN, Phillip, John [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). MEUDT, Andreas [DE/DE]; Clariant GmbH, 65843 Sulzbach (DE).
- (74) Agent: ASTRAZENECA; Global Intellectual Property, S-SE-151 85 Sodertalje (SE).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

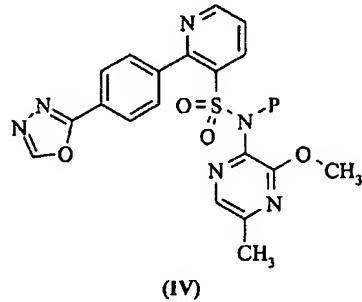
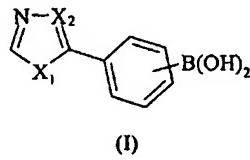
## Published:

- without international search report and to be republished upon receipt of that report

*[Continued on next page]*

(54) Title: CHEMICAL PROCESS

WO 2005/080403 A2



(57) Abstract: Process for preparing compounds of Formula (I); and (IV); are described.



*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

- 1 -

### CHEMICAL PROCESS

The present invention relates to an improved chemical process for preparing intermediates. Certain of these intermediates are useful in the manufacture of compounds 5 which are useful in the treatment of, for example, cancer, pain and cardiovascular diseases in a warm-blooded animal such as man, particularly compounds which possess endothelin receptor antagonist activity.

In particular, the present invention relates to a chemical process for preparing [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid which is used in the manufacture of 10 N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide which compound is disclosed as Example 36 of International Patent Application WO96/40681. This compound possesses endothelin receptor antagonist activity, and accordingly is useful whenever such antagonist activity is desired, such as for research tools within pharmacological, diagnostic, and related studies or in the treatment of diseases 15 and medical conditions including, but not limited to hypertension, pulmonary hypertension, cardiac or cerebral circulatory disease and renal disease. In addition this compound is also useful in the treatment of cancer and pain, in a warm-blooded animal such as man.

A route for preparing N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl] phenyl)pyridine-3-sulphonamide is disclosed in International Patent Applications 20 WO 96/40681 and WO 98/40332. The route involves the use of the compound N-(isobutoxycarbonyl)-2-(4-methoxycarbonylphenyl)-N-(3-methoxy-5-methylpyrazin-2-yl)pyridine-3-sulphonamide as an intermediate with the formation of the 1,3,4-oxadiazole in the 4-position of the phenyl group occurring at the end of the synthesis. This existing route is satisfactory for the synthesis of relatively small amounts of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide but is a linear rather than 25 convergent synthesis, involving the isolation of a substantial number of intermediates. As such, the overall yield of this synthesis is not high.

Furthermore, as the heteroaryl moiety at the 4-position of the phenyl group is formed as the last step, it is necessary to undergo a linear synthesis approach with the rest of the 30 molecule made first. This is clearly undesirable when substituents in distinct parts of the molecule need to be varied in order to investigate structure-activity relationships. It would be highly desirable if a convergent approach to the synthesis of this type of compound could be devised. This would also be of significant benefit in the efficiency of manufacturing large

- 2 -

scale amounts of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide.

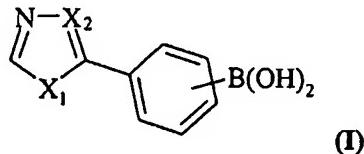
We have now devised a much improved process for the manufacture of heteroaryl-phenyl boronic acids, in particular, [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid.

- 5 The process allows exploitation of a more convergent route to N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide than the previously described route and allows a reduction in the number of intermediates that must be isolated. This provides significant advantages of time and cost of manufacture.

- In a further aspect of the present invention one of the heteroaryl-phenyl boronic acids,
- 10 [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid, produced according to the present invention, is used to prepare *N*-protected N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamides, in particular N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide. These intermediates may then be deprotected to form N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide.

- The process for the manufacture of heteroaryl-phenyl boronic acids of the present invention utilises the increased acidity of the heteroaryl ring proton, and involves the sequential use of two bases. Initial attempts at adding one equivalent of a base to a heteroaryl-phenyl bromo compound in order to induce halogen-metal exchange led to competing deprotonation of the heteroaryl ring. On quenching with a borate ester, a negligible yield of the desired product was achieved, together with starting material and by-products. The present inventors found, surprisingly, that the sequential use of two bases leads to good yields of the desired heteroaryl-phenyl boronic acids. In the process of the present invention the heteroaryl ring is initially deprotonated with a (typically) "weaker" base, before inducing halogen-metal exchange with a (typically) "stronger" base.

According to a first aspect of the present invention, there is provided a process for the preparation of a compound of the Formula I



wherein,

- 30 X<sub>1</sub> is selected from O, NR<sub>1</sub> or S; and

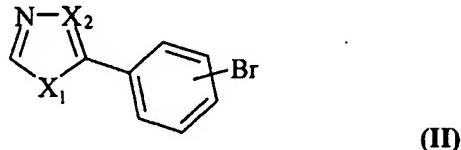
- 3 -

$X_2$  is selected from CH or N;

wherein  $R_1$  is a nitrogen-protecting group,

which comprises :-

the sequential reaction of a compound of the Formula II



5

with,

- (i)      methyl- or an optionally substituted aryl- lithium; and then
- (ii)     n-butyl-, s-butyl-; t-butyl- or n-hexyl- lithium; and then
- (iii)    a borate ester.

10       For process steps (i), (ii) and (iii), the reactions may conveniently be carried out in an inert solvent or diluent or an ethereal solvent such as diethyl ether, tetrahydrofuran, diethoxymethane, 1,2-dimethoxyethane or 1,4-dioxan. Thus, for example, the reaction may be carried out by sequentially treating 2-(4-bromophenyl)-1,3,4-oxadiazole with 4-methylphenyllithium, followed by n-hexyllithium, and finally triisopropylborate in a  
15      suitable solvent or diluent, for example, an ethereal solvent such as tetrahydrofuran, at a temperature in the range, for example, -90 to -50°C, more particularly -70 to -55°C, conveniently at or near -70°C.

20       Optionally the heteroaryl-phenyl bromo compound of Formula II can be charged to a solution of the first base to enable deprotonation, followed by the addition of the second base to induce transmetalation. This method although slightly less efficient in yield and quality does have advantages in cases where the first base must be generated in situ due to lack of stability at ambient temperatures. In this case only one cryogenic vessel is required to complete the processing.

25       The molar ratios of the reagents used in process steps (i), (ii), and (iii), are preferably in the range from 1.0-1.5: 1.0-1.5: 2.1-3 respectively, but more preferably in the range 1.06-1.3: 1.07-1.1: 2.2-2.3 respectively. Conveniently, the lithiated intermediates formed during the conversion of compounds of the Formula II to compounds of Formula I are not isolated as such but are each prepared and used as a solution in an organic solvent. Thereby, compounds of Formula I may be manufactured from compounds of Formula II in a one-pot  
30      procedure.

- 4 -

An aryl lithium is, for example, phenyl or naphthyl- lithium.

An optional substituent for an aryl lithium is, for example, methyl.

Particularly preferred optionally substituted aryl lithiums are, for example, phenyl-, 2-methylphenyl-, 4-methylphenyl-, mesityl- or naphthyl- lithium.

5 A borate ester is an alkyl, alkenyl or aryl boronic ester, for example, trimethyl-, triethyl- or triisopropyl- borate.

When R<sub>1</sub> is a nitrogen-protecting group, then, for example, suitable methods for protection are those known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups

10 in Organic Synthesis, John Wiley and Sons, 1991).

A suitable nitrogen- protecting group, R<sub>1</sub>, is, for example, an (1-6C)alkyl, phenyl, allyl, methoxymethyl, benzyl, triphenylmethyl or diphenylphosphinyl protecting group.

This first aspect of the present invention provides compounds of Formula I in commercially acceptable yields and of high quality.

15 Further values of X<sub>1</sub> and X<sub>2</sub> are as follows. Such values may be used where appropriate with any definitions, claims or embodiments defined hereinbefore or hereinafter.

X<sub>1</sub> is O.

X<sub>1</sub> is NR<sub>1</sub>.

X<sub>1</sub> is S.

20 X<sub>2</sub> is CH.

X<sub>2</sub> is N.

X<sub>1</sub> is O, and X<sub>2</sub> is CH.

X<sub>1</sub> is O, and X<sub>2</sub> is N.

X<sub>1</sub> and X<sub>2</sub> are N.

25 X<sub>1</sub> is NR<sub>1</sub>, and X<sub>2</sub> is CH.

X<sub>1</sub> is NR<sub>1</sub>, and X<sub>2</sub> is N.

X<sub>1</sub> is S and X<sub>2</sub> is CH.

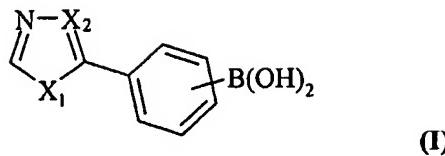
X<sub>1</sub> is S and X<sub>2</sub> is N.

R<sub>1</sub> is allyl or benzyl.

30 R<sub>1</sub> is benzyl.

Therefore in an additional aspect of the invention there is provided a process for the preparation of compounds of the Formula I

- 5 -



(I)

wherein,

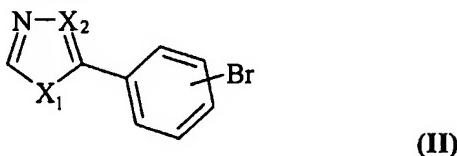
X<sub>1</sub> is selected from O, NR<sub>1</sub> or S; and

X<sub>2</sub> is selected from CH or N;

5 wherein R<sub>1</sub> is a nitrogen-protecting group;

which comprises :-

the sequential reaction of compounds of the Formula II

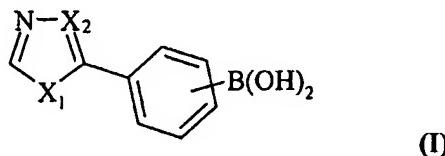


(II)

with,

- 10 (i) 4-methylphenyllithium; and then
- (ii) n-hexyllithium; and then
- (iii) triisopropylborate.

In a further aspect of the invention there is provided a process for the preparation of compounds of the Formula I



(I)

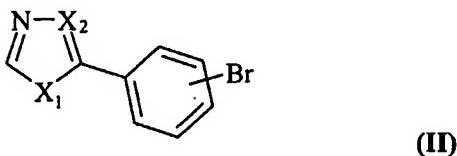
wherein,

X<sub>1</sub> is selected from O, NR<sub>1</sub> or S; and

X<sub>2</sub> is selected from CH or N;

wherein R<sub>1</sub> is a nitrogen-protecting group; which comprises :-

20 the sequential reaction of compounds of the Formula II



(II)

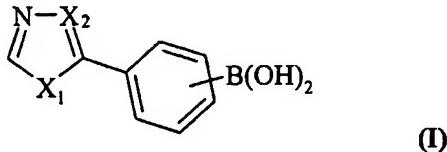
with,

- (i) methyllithium; and then

- 6 -

- (ii) n-hexyllithium; and then
- (iii) triisopropylborate.

In a further aspect of the invention there is provided a process for the preparation of compounds of the Formula I



5

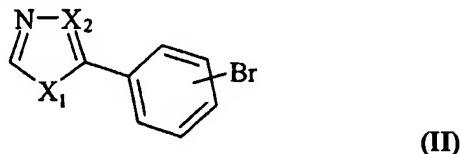
wherein,

X<sub>1</sub> is O; and

X<sub>2</sub> is N;

which comprises :-

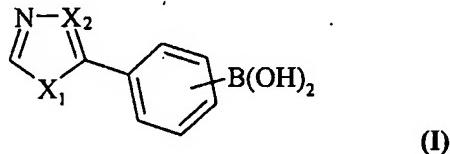
10 the sequential reaction of compounds of the Formula II



with,

- (i) methyllithium; and then
- (ii) n-butyllithium; and then
- 15 (iii) triisopropylborate.

In a further aspect of the invention there is provided a process for the preparation of compounds of the Formula I,



wherein,

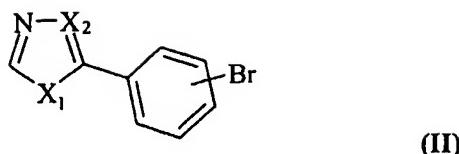
20 X<sub>1</sub> is O; and

X<sub>2</sub> is N;

which comprises :-

the sequential reaction of compounds of the Formula II

-7-



with.

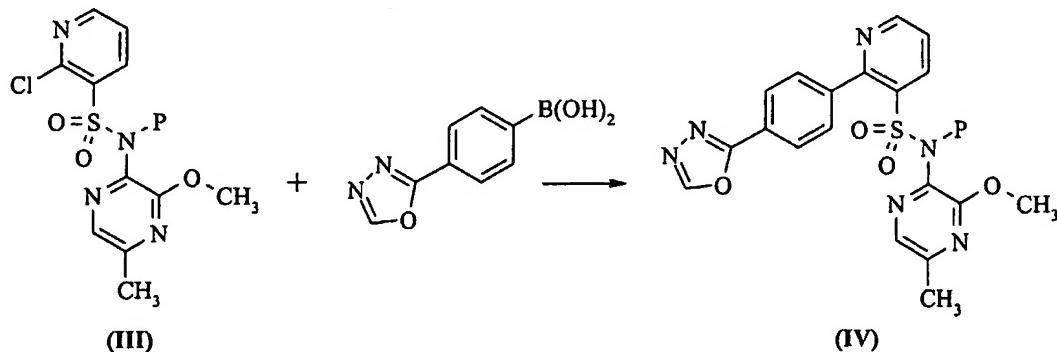
- (i) 4-methyphenyllithium; and then  
 (ii) n-butyllithium; and then  
 5 (iii) triisopropylborate.

Compounds of the formula (II) may be prepared according to the experimental methods and procedures disclosed in *Bioorganic & Medicinal Chemistry Letters*, 2002, 12(20), 2879-2882; *Eur. J. Med. Chem.*, 2000, 35, 157-162; *Helvetica Chimica Acta*, 1950, 33, 1271-1276; *Eur. J. Med. Chem.*, 1985, 20(3), 257-66 and *J. Het. Chem.*, 1989, 26, 1341.

10 A further aspect of the present invention provides the use of [4-(1,3,4-oxadiazol-2-yl)phenyl] boronic acid, prepared according to the present invention, in the preparation of compounds of Formula IV which are intermediates useful in the preparation of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide.

N-(3-Methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide is prepared by deprotecting compounds of Formula IV.

In this aspect of the invention [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid is coupled with compounds of Formula III to form compounds of Formula IV.



Particularly this reaction takes place in an aqueous solvent, for example methanol,  
20 ethanol, isopropanol, industrial methylated spirit (IMS), isobutanol, NMP  
(N-methylpyrrolidinone), DMF; with or without an organic phase, for example toluene or  
xylenes at a temperature in the range, for example 60 to 100°C more particularly 75 to 85°C,  
in the presence of:

- (i) the boronic acid

- 8 -

- (ii) a suitable source of palladium (0), for example  $\text{PdCl}_2$ ,  $\text{Pd}(\text{Ph}_3\text{P})_4$  or  $\text{Pd}(\text{OAc})_2$ ;
- (iii) a suitable ligand, for example triphenylphosphine or 3,3',3"-phosphinidyne tris(benzenesulphonic acid) trisodium salt;
- (iv) a base, for example triethylamine, benzylidemethylamine, N-methylmorpholine, N-methylpiperidine, triethanolamine, ethyldiethanolamine, diisopropylethylamine, potassium acetate, cesium fluoride or potassium fluoride.

Particularly the source of palladium is palladium acetate.  
Particularly the base is N-methylmorpholine. In another aspect, particularly the base is triethylamine.

Particularly this reaction takes place in an aqueous solvent without an organic phase.  
In another aspect, particularly this reaction takes place in an aqueous solvent with an organic phase. Where this reaction takes place in an aqueous solvent with an organic phase, particularly the organic phase comprises toluene. In another aspect of the present invention, where this reaction takes place in an aqueous solvent with an organic phase, particularly the organic phase comprises xylene.

In another aspect, this reaction more specifically takes place in the presence of palladium acetate, 3,3',3"-phosphinidyne tris(benzenesulphonic acid) trisodium salt, N-methylmorpholine in water and isopropanol.

In another aspect, this reaction more specifically takes place in the presence of palladium acetate, 3,3',3"-phosphinidyne tris(benzenesulphonic acid) trisodium salt, triethylamine, xylene, water and IMS.

The molar ratios of the reagents used in process steps (i), (ii), (iii) and (iv), are preferably in the range from 1.0-2.0: 0.02-0.3: 0.06-0.9: 1.5-5.0 respectively, but more preferably in the range 1.4-1.6: 0.03-0.1: 0.09-0.3: 2.0-3.0 respectively.

In compounds of Formula III or Formula IV, P is a nitrogen-protecting group. Suitable methods for protection are those known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley and Sons, 1991).

A suitable value for P is, for example, an acyl group, for example a C<sub>1-6</sub>alkanoyl group such as acetyl; an aryl group, for example benzoyl; a C<sub>1-6</sub>alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, isobutoxycarbonyl or *tert*-butoxycarbonyl group; an

- 9 -

arylmethoxycarbonyl group, for example benzyloxycarbonyl; a phosphinyl group, for example diphenylphosphinyl; a benzyl group or a C<sub>2-6</sub>alkenyl group such as allyl.

A suitable value for P is a C<sub>1-6</sub>alkoxycarbonyl group. More suitable values for P are a methoxycarbonyl, ethoxycarbonyl or isobutoxycarbonyl group. More specifically a value for 5 P is isobutoxycarbonyl.

The deprotection conditions for the nitrogen protecting groups described herein necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as a C<sub>1-6</sub>alkanoyl or a C<sub>1-6</sub>alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or 10 sodium hydroxide or an amine, for example ammonia. Alternatively an alkoxy carbonyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with 15 a Lewis acid for example boron tris(trifluoroacetate). A phosphinyl group may be removed by base hydrolysis such as an alkali metal hydroxide, for example lithium or sodium hydroxide or an amine, for example ammonia. A benzyl group may be removed by hydrogenation over a catalyst such as palladium-on-carbon. A C<sub>2-6</sub>alkenyl group such as allyl may be removed palladium assisted hydrolysis.

20 In a further aspect of the invention there is provided a process for preparing a compound of Formula IV which comprises reacting [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid with a compound of Formula III.

In a further aspect of the invention there is provided a process for preparing a compound of Formula IV which comprises reacting [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid, prepared according to the present invention, with a compound of Formula III.

In this aspect of the invention, more specifically the invention provides the use of [4-(1,3,4-oxadiazol-2-yl)phenyl] boronic acid, prepared according to the present invention, in the preparation of N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide a compound of Formula IV and an 30 intermediate useful in the preparation of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl] phenyl)pyridine-3-sulphonamide.

In this aspect of the invention [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid is coupled with N-(isobutoxycarbonyl)-2-chloro-N-(3-methoxy-5-methylpyrazin-2-yl) pyridine-3-

- 10 -

sulphonamide to form N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide.

The preparation of N-(isobutoxycarbonyl)-2-chloro-N-(3-methoxy-5-methylpyrazin-2-yl) pyridine-3-sulphonamide is described in Example 1 of WO96/40681.

5 Thus according to this aspect of the invention there is provided a process for preparing N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide which comprises coupling [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid with N-(isobutoxycarbonyl)-2-chloro-N-(3-methoxy-5-methylpyrazin-2-yl) pyridine-3-sulphonamide.

10 Therefore in a further aspect of the invention there is provided the use of [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid in the preparation of N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide.

In a further aspect of the invention there is provided the use of  
15 [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid, prepared according to the process of the present invention, in the preparation of N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide.

In a further aspect of the invention there is provided a compound of Formula IV.  
In a further aspect of the invention there is provided N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide.

In a further aspect of the invention there is provided the use of N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide in the preparation of N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl] phenyl)pyridine-3-sulphonamide.

25 The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

- (i) yields are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;
- (ii) <sup>1</sup>H NMR spectra were determined at either 270MHz or 400MHz in DMSO<sub>d</sub><sub>6</sub> using  
30 tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d, doublet.

- 11 -

**Example 1**

**[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid**

A solution of methylolithium (8% w/w in diethoxymethane) (65 ml) was added to a suspension of 2-(4-bromophenyl)-1,3,4-oxadiazole (40 g) in tetrahydrofuran (THF) (415 ml) at -65°C.

- 5 After an hour a solution of n-butyllithium (2.5M in hexanes) (78 ml) was then added at -65°C. After an hour, triisopropylborate (90 ml)) was then added maintaining the reaction mixture at -65°C. The reaction mixture was held at -65°C for an hour and then warmed to -20°C and drowned out into a mixture of acetic acid (28 ml) in water (222 ml). The resultant solid was isolated, washed with THF and water, and dried to yield the title compound (28.96 g @ 10 95.1% w/w, 82%); 400MHz NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 8.00 (s, 4H), 8.31 (s, 2H), 9.35 (s, 1H); Mass Spectrum MH<sup>+</sup> 191.0628 (calc. using 11-B) Found 191.0633.

The 2-(4-bromophenyl)-1,3,4-oxadiazole used as a starting material was prepared as follows:

- To a suspension of 4-bromobenzoic hydrazide (200 g) in industrial methylated spirit (700 ml) was added triethylorthoformate (309 ml), industrial methylated spirit (100 ml) and sulphuric acid (0.8 ml). The reaction mixture was heated to reflux for 1 hour. The reaction mixture was cooled to 0-5°C and product crystallised. Product was isolated, washed and dried to yield 2-(4-bromophenyl)-1,3,4-oxadiazole (186.1 g, 89.9%). 400MHz NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 9.35 (s, 1H), 7.98 (d, 1H), 7.95 (d, 1H), 7.84 (d, 1H), 7.81 (d, 1H); Mass Spectrum 20 MH<sup>+</sup> 224.9663 (calc. using 79-Br) Found 224.9701.

**Example 2**

**[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid**

- Lithium granules (8.2 g) and tetrahydrofuran (670 g) were charged to a reactor under an argon atmosphere and the mixture cooled to -35°C. 4-Chlorotoluene (74.3 g) was added at -35°C and the mixture was held at this temperature for 6 hours. The resultant solution was added to a suspension of 2-(4-bromophenyl)-1,3,4-oxadiazole (124.4 g) in tetrahydrofuran (800 g) at -65°C. After 30 mins a solution of n-hexyllithium (33%w/w in hexanes) (240ml) was then added at -65°C. After a futher 30 min triisopropylborate (230.8 g) was then added 30 maintaining the reaction mixture at -65°C. The reaction mixture was allowed to warm to -35°C and drowned out into a solution of acetic acid (91.5 g) in water (688 g). The resultant

- 12 -

solid was isolated, washed with THF and water, and dried to yield the title compound (92.2 g, 88%).

**Example 3**

5 **[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid**

Example 2 was repeated but the charge of 4-chlorotoluene increased from 1.06 moles to 1.30 moles. The yield of the title compound increased to 89.3%.

**Example 4**

10 **[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid**

Tetrahydrofuran (250 g) was charged to a mixture of lithium granules (3.02 g) and biphenyl (0.01 g) under an argon atmosphere and the mixture cooled to -30°C. 2-Chlorotoluene (27.55 g) was slowly added at -30°C. The reaction was held at -30°C for 6 hours and then cooled to -65°C. A mixture of 2-(4-bromophenyl)-1,3,4-oxadiazole (50.0 g) in THF (300 g) was slowly added at -65°C. The reaction was held at -65°C for 30 minutes then a solution of n-hexyllithium (33%w/w in hexanes, 86 ml) was added at -65°C. The reaction was held at -65°C for 30 minutes and then trimethylborate (48.7 g) was added at -65°C. The reaction was held at -65°C for 10 minutes then methanol (55.3 g) was added followed by 4-methyl-2-pentanone (240 g). The reaction mixture was warmed and the low boiling solvents distilled off under vacuum to a maximum temperature of 55°C. The residual mixture was cooled to 0°C and 10%w/w sulphuric acid (92 g) was added followed by water (92 g) whilst maintaining the temperature below 7°C. Product precipitated. The pH was adjusted to 6.5 by the addition of more 10%w/w sulphuric acid (85.3 g). The mixture was heated to 40°C then cooled back to 5-10°C. Product was isolated and washed with THF (56g) and water (60g), yielding wet title compound (25.2 g, 60%).

**Example 5**

**[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid**

Tetrahydrofuran was charged to lithium granules (7.6 g) under an argon atmosphere and the mixture cooled to -30°C. 2-Chlorotoluene (69.4 g) was slowly added at -30°C. The reaction was held at -30°C for 6 hours then added to a suspension of 2-(4-bromophenyl)-1,3,4-oxadiazole (124.4 g) in tetrahydrofuran (800 g) at -65°C. The

- 13 -

reaction was held at -65°C for 30 minutes then a solution of n-hexyllithium (33%w/w in hexanes, 245 ml) was added at -65°C. The reaction was held at -65°C for 30 minutes and then trimethylborate (230.8 g) was added at -65°C. The reaction was held at -65°C for 30 minutes then methanol (175 ml) was added followed by 4-methyl-2-pentanone (600 g). The reaction  
5 mixture was warmed and the low boiling solvents distilled off under vacuum to a maximum temperature of 50°C. The reaction mixture was cooled to 5-10°C and the pH adjusted to 6.5 by the addition of 5%w/w sulphuric acid (990.5 g). Product precipitated. The mixture was heated to 40°C then cooled back to 10°C. Product was isolated, washed with THF and water, and dried yielding the title compound (79.3 g, 75.5%).

10

**Example 6**

**[4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid**

Example 4 was repeated but chlorobenzene (61.6 g) was used instead of 2-chlorotoluene. The isolated yield of the title compound was 87.8 g, (83.8%).

15

**Example 7**

**N-(Isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide**

Palladium acetate (0.4144g) and 3,3',3''-phosphinidyne tris(benzenesulphonic acid)  
20 trisodium salt 30% w/w aq sol (3.26g) were dissolved in water (35ml) over 6 minutes in an ultrasonic bath. The yellow solution was added to a stirred slurry of [4-(1,3,4-oxadiazol-2-yl)phenyl] boronic acid (10g) and isobutyl [(2-chloropyridin-3-yl)sulfonyl](3-methoxy-5-methylpyrazin-2-yl)carbamate (16.86g) in xylene (100ml), industrial methylated spirit (50ml) and triethylamine (17ml). The catalyst dissolution flask  
25 was then washed in with water (5ml) and the reaction mixture heated to reflux (80°C) on an oil bath (105°C) and stirred at reflux for 24.5 hours. The reaction mixture was cooled to 30°C and filtered through a Whatman GF/B glass filter paper and the lower aqueous phase separated off. The reaction flask and filter cake was washed with xylene (20ml). The xylene wash was used to re-extract the aqueous phase. The combined organic phases were stirred and  
30 heated to reflux (85°C) in a clean 500ml 4-necked flask equipped with overhead stirrer, water condenser, and nitrogen atmosphere. Essochem solvent 30 (hydrocarbons Bp 100-130°C) (100ml) was added dropwise over 6 min and the mixture was allowed to self cool to ambient temperature and then further cooled to -5°C and held for 1 hour. The product was filtered off

- 14 -

and washed with Essochem solvent 30 (50ml). The cake was dried on the filter for 3 hours to give 15.20g @100% strength, yield 76.8%. 270 MHz <sup>1</sup>H-NMR Spectrum: 0.70 (d, 6H), 1.72 (m, 1H), 2.51 (s, 3H), 3.84 (d, 2H), 4.00 (s, 3H), 7.59 (m, 1H); 7.80 (d, 2H), 7.90 (s, 1H), 8.17 (d, 2H), 8.50 (s, 1H), 8.90 (m, 1H) and 9.00 (d, 1H). Mass Spectrum MH<sup>+</sup> = 525.2  
5 (C<sub>24</sub>H<sub>25</sub>N<sub>6</sub>O<sub>6</sub>S = 525.16).

#### Example 8

##### N-(Isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide

- 10 To a nitrogen purged 500mL multi necked flask equipped with an overhead stirrer was charged isobutyl [(2-chloropyridin-3-yl)sulfonyl](3-methoxy-5-methylpyrazin-2-yl)carbamate (22.15g), [4-(1,3,4-oxadiazol-2-yl)phenyl] boronic acid (12.26g), isopropanol (60ml), water (140ml) and 3,3',3''-phosphinidyne tris(benzenesulphonic acid) trisodium salt 30% w/w aq sol (13.7g). Agitation was started and palladium acetate (0.541g) was added after 10 minutes.
- 15 N-Methylmorpholine (13.25ml) was added and the temperature was adjusted to 80°C. After 4h 20min toluene (140ml) was added and the temperature adjusted to 60°C. After a further 45 min the mixture was filtered through a 1μm glass fibre filter paper and the aqueous phase separated off. The reaction flask and filter cake was washed with toluene (22ml). The toluene wash was used to re-extract the aqueous phase and the organic layers were combined. These 20 contained the title compound (22.8g, 90%) which was not isolated.

#### Example 9

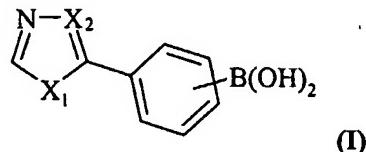
##### N-(Isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide

- 25 To a nitrogen purged 150ml multi necked flask equipped with an overhead stirrer was charged isobutyl [(2-chloropyridin-3-yl)sulfonyl](3-methoxy-5-methylpyrazin-2-yl)carbamate (7.75g), [4-(1,3,4-oxadiazol-2-yl)phenyl] boronic acid (4.29g), isopropanol (21ml), water (49ml) and 3,3',3''-phosphinidyne tris(benzenesulphonic acid) trisodium salt 30% w/w aq sol (2.88g). Agitation was started and palladium acetate (0.114g) was added after 10 minutes. Potassium 30 fluoride (2.48g) was added and the temperature was adjusted to 80°C. After 5h toluene (49ml) was added and the temperature adjusted to 60°C. After a further 10min the mixture was filtered through a 1μm glass fibre filter paper and the aqueous phase separated off. The organic phase contained the title compound (7.36g, 83%) which was not isolated.

- 15 -

**CLAIMS**

1. A process for the preparation of a compound of the Formula I



5 wherein,

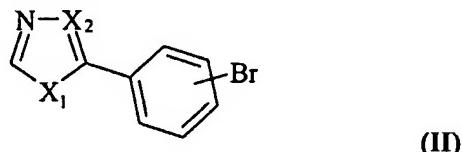
$X_1$  is selected from O,  $NR_1$  or S; and

$X_2$  is selected from CH or N;

wherein  $R_1$  is a nitrogen-protecting group,

which comprises :-

- 10 the sequential reaction of a compound of the Formula II



with,

- (i) methyl- or an optionally substituted aryl- lithium; and then
- (ii) n-butyl-, s-butyl-, t-butyl- or n-hexyl- lithium; and then
- 15 (iii) a borate ester.

2. The process according to claim 1 wherein  $X_1$  is O.

3. The process according to claim 1 or 2 wherein  $X_2$  is N.

- 20 4. The process according to any one of claims 1-3 wherein said methyl- or an optionally substituted aryl- lithium is 4-methylphenyllithium or methyllithium.

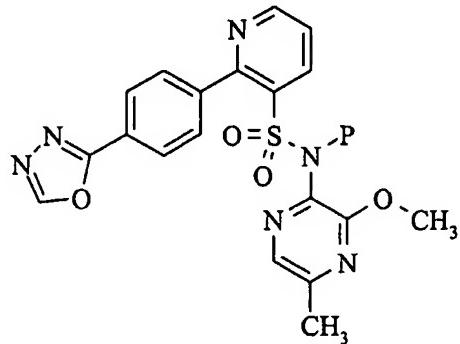
5. The process according to any one of claims 1-4 wherein said n-butyl-, s-butyl-,  
25 t-butyl- or n-hexyl- lithium is n-hexyllithium or n-butyllithium.

6. The process according to any one of claims 1-5 wherein said borate ester is triisopropylborate.

- 16 -

7. [4-(1,3,4-Oxadiazol-2-yl)phenyl]boronic acid prepared by the process as claimed in any one of claims 1-6.

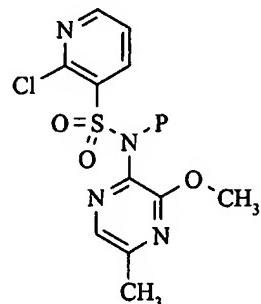
8. A process for preparing compounds of Formula IV:



(IV)

5

which comprises coupling [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid with a compound of Formula III:



(III)

whercin P is a nitrogen-protecting group.

10

9. The process according to claim 8 which takes place in the presence of

- (i) a source of palladium (0) selected from  $\text{PdCl}_2$ ,  $\text{Pd}(\text{Ph}_3\text{P})_4$  or  $\text{Pd}(\text{OAc})_2$ ;
- (ii) a suitable ligand selected from triphenylphosphine or 3,3',3"-phosphinidyne tris(benzenesulphonic acid) trisodium salt;

15

- (iii) a base selected from triethylamine, benzyltrimethylamine, N-methylmorpholine, N-methylpiperidine, triethanolamine, ethyldiethanolamine, diisopropylethylamine, potassium acetate, cesium fluoride or potassium fluoride.

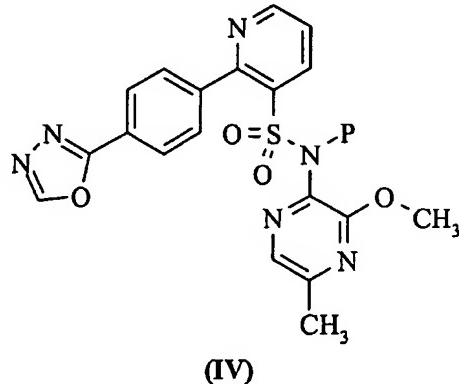
- 17 -

10. The process according to claim 8 or claim 9 wherein said [4-(1,3,4-oxadiazol-2-yl)phenyl]boronic acid is prepared according to the process as claimed in any one of claims 1-7.

11. The process according to any one of claims 8 - 10 wherein P is isobutoxycarbonyl.

5

12. A compound of Formula IV:



wherein P is a nitrogen-protecting group.

10 13. A compound of Formula IV as claimed in claim 11 which is N-(isobutoxycarbonyl) N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl) pyridine-3-sulphonamide.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

**(19) World Intellectual Property Organization  
International Bureau**



A standard linear barcode is located at the bottom of the page, spanning most of the width. It is used for tracking and identification of the publication.

**(43) International Publication Date  
1 September 2005 (01.09.2005)**

PCT

(10) International Publication Number  
**WO 2005/080403 A3**

(51) International Patent Classification<sup>7</sup>: C07F 5/02,  
C07D 401/14 Philip, John [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). MEUDT, Andreas [DE/DE]; Clariant GmbH, 65813 Sulzbach (DE)

**(21) International Application Number:**

PCT/GB2005/000567

**Philip, John [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). MEUDT, Andreas [DE/DE]; Clariant GmbH, 65843 Sulzbach (DE).**

(22) International Filing Date: 17 February 2005 (17.02.2005)

**(25) Filing Language:**

English

**(26) Publication Language:**

English

**(30) Priority Data:**

0403744.6 20 February 2004 (20.02.2004) GB

(71) Applicant (for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only): ASTRAZENECA AB [SE/SE]; S-SE-151 85 Sodertalje (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

**(72) Inventors; and**

(75) Inventors/Applicants (*for US only*): BUTLIN, Margaret, Anne [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). BUTLIN, Roger, John [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). HOGAN,

(74) Agent: ASTRAZENECA; Global Intellectual Property,  
S-SE-151 85 Sodertalje (SE).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

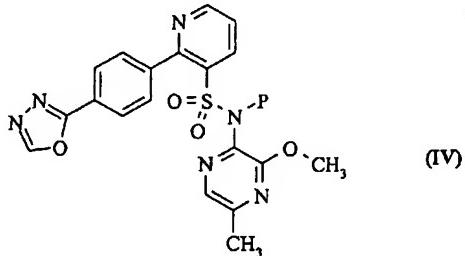
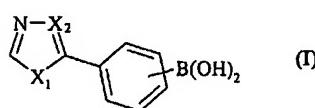
**Published:**

— with international search report

(88) Date of publication of the international search report:  
24 November 2005

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**(54) Title: CHEMICAL PROCESS**



WO 2005/080403 A3

(57) Abstract: Process for preparing compounds of Formula (I); and (IV); are described.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2005/000567

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07F5/02 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 197 967 B1 (VOLLMUELLER FRANK ET AL) 6 March 2001 (2001-03-06) claim 1; example 5; table 5 -----	7
A		1-6
X	PIETTRE S R ET AL: "Monoaryl- and Bisarylhydroxytropolones as Potent Inhibitors of Inositol Monophosphatase" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 40, 1997, pages 4208-4221, XP002329872 ISSN: 0022-2623 page 4214, right-hand column, paragraph 2 - paragraph 6; compounds 20J, 1P page 4216, left-hand column, paragraph 3 ----- -/-	1-7

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

9 August 2005

Date of mailing of the International search report

29.08.2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl  
Fax: (+31-70) 340-3016

Authorized officer

Härtinger, S

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2005/000567

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>a</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/40332 A (ZENECA LIMITED; HOGAN, PHILIP, JOHN) 17 September 1998 (1998-09-17) cited in the application page 5, line 20 – line 26 page 7, line 5 – line 10	1-7
X		8-13
A	WO 96/40681 A (ZENECA LIMITED) 19 December 1996 (1996-12-19) cited in the application page 17, paragraph 2; claim 15; example 36	1-7
X	page 16, last paragraph page 19, paragraph 1	8-13

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2005/000567

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7

synthesis of azole substituted phenylboronic acids  
-----

2. claims: 8-13

preparation of oxadiazole coupling products  
-----

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

Inte	al Application No
PCT/GB2005/000567	

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
US 6197967	B1	06-03-2001	DE GB	19857765 A1 2344817 A	21-06-2000 21-06-2000
WO 9840332	A	17-09-1998	AT AU DE EP ES WO JP US US ZA	278651 T 6630098 A 69826845 D1 0973704 A1 2227807 T3 9840332 A1 2001514648 T 2003162973 A1 6531605 B1 9801933 A	15-10-2004 29-09-1998 11-11-2004 26-01-2000 01-04-2005 17-09-1998 11-09-2001 28-08-2003 11-03-2003 07-09-1998
WO 9640681	A	19-12-1996	AT AU AU BR CA CN CZ DE DE DK EP ES WO HK HR HU IL JP JP NO NZ PL PT SI SK TR US US US ZA	209200 T 715041 B2 5840396 A 9608611 A 2219742 A1 1192739 A ,C 9703887 A3 69617236 D1 69617236 T2 832082 T3 0832082 A1 2168487 T3 9640681 A1 1005801 A1 960272 A1 9802300 A2 122464 A 11509175 T 3193058 B2 975700 A 308619 A 324660 A1 832082 T 832082 T1 168097 A3 9701502 T1 6060475 A 6258817 B1 5866568 A 9604615 A	15-12-2001 13-01-2000 30-12-1996 11-05-1999 19-12-1996 09-09-1998 18-03-1998 03-01-2002 11-07-2002 21-05-2002 01-04-1998 16-06-2002 19-12-1996 20-12-2002 31-08-1997 28-10-1999 23-05-2002 17-08-1999 30-07-2001 05-12-1997 28-01-2000 08-06-1998 29-04-2002 30-04-2002 06-05-1998 21-03-1998 09-05-2000 10-07-2001 02-02-1999 09-12-1996